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STATE-OF-THE-ART REVIEW

Antithrombotic Management of Elderly Patients With Coronary Artery Disease

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ABSTRACT

Antithrombotic therapy represents the mainstay of treatment in patients with coronary artery disease (CAD), including elderly patients who are at increased risk for ischemic recurrences. However, the elderly population is also more vulnerable to bleeding complications. Numerous mechanisms, including abnormalities in the vasculature, thrombogenicity, comorbidities, and altered drug response, contribute to both increased thrombotic and bleeding risk. Age-related organ changes and drug-drug interactions secondary to polypharmacy lead to distinct pharmacokinetic and pharmacodynamic profiles of antithrombotic drugs. Overall these factors contribute to the risk-benefit profiles of antithrombotic therapies in elderly subjects and underscore the need for treatment regimens that can reduce bleeding while preserving efficacy. Given that the prevalence of CAD, as well as concomitant diseases with thromboembolic potential, such as atrial fibrillation, increases with age and that the elderly population is in continuous growth, understanding the safety and efficacy of different antithrombotic regimens is pivotal for patient-centered care. In the present overview the authors appraise the available data on the use of antithrombotic therapy in older patients with CAD to assist with the management of this high-risk population and define knowledge gaps that can set the basis for future research. (J Am Coll Cardiol Intv 2021;14:723–38)

The increase in life expectancy in developed countries has led to a growth of the elder population (1). However, aging increases the risk for cardiovascular morbidity, with coronary artery disease (CAD) being the most common manifestation and leading cause of death (2,3). Therefore, elderly patients with CAD manifestations, including chronic coronary syndrome (CCS) and acute coronary syndrome (ACS), many of whom undergo percutaneous coronary intervention (PCI), are commonly encountered in clinical practice. Importantly, elderly patients frequently have concomitant comorbid conditions that can affect response to antithrombotic therapies indicated for preventing ischemic recurrences (2,3). Indeed, elderly patients have an increased risk for both thrombotic and bleeding events, which may be enhanced by the coexistence of other conditions such as atrial fibrillation (AF) requiring specific antithrombotic regimens (i.e., oral anticoagulants [OACs]) (2–4). Therefore, understanding the impact of age on the safety and efficacy of different antithrombotic regimens is pivotal for a patient-centered care approach. In the present overview we appraise the available data and current recommendations on the use of antithrombotic therapies in elderly patients with CAD.

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)

AF = atrial fibrillation

CAD = coronary artery disease

CCS = chronic coronary syndrome(s)

DAPT = dual-antiplatelet therapy

DAT = double-antithrombotic therapy

HBR = high bleeding risk

HPR = high platelet reactivity

OAC = oral anticoagulant

PCI = percutaneous coronary intervention

PFT = platelet-function testing

RRR = relative risk reduction

VKA = vitamin K antagonist

MECHANISMS OF THROMBOSIS AND BLEEDING IN ELDERLY PATIENTS

Several mechanisms contribute to the increased risk for both ischemic and bleeding events in the elderly population (**Figure 1**) (2,3). The hemostatic imbalance toward increased clotting and decreased fibrinolysis, blood stasis, endothelial dysfunction, vessel inflammation, and increased platelet reactivity may contribute to their enhanced thrombotic risk (5–7). In contrast, age-related collagen and amyloid deposits in the arterial wall weaken the vessel, predisposing to bleeding (8). Comorbidities commonly encountered in elderly patients can further increase bleeding and thrombotic risk (**Figure 1**). In particular, frequent chronic conditions including renal dysfunction, anemia, cancer, and inflammatory diseases, along with the excessive use of nonsteroidal anti-inflammatory drugs and issues related to the greater risk for falls, are all factors increasing both bleeding and thrombotic complications in elderly patients, thus warranting a careful individualized balance of the benefit and risk of antithrombotic therapies. Moreover, changes in organ function, poor medication adherence, and polypharmacy-related drug interactions can affect pharmacokinetic and pharmacodynamic responses to antithrombotic drugs (**Figure 2**) (2,3). Of note, elderly patients have unique features (i.e., forgetfulness, fallibility, misconceptions, depression, cognitive impairment, polypharmacy) related to high risk for suboptimal drug adherence that can lead to both under- and overtreatment. In the following sections, we provide an overview of the safety and efficacy profiles of oral antithrombotic agents in elderly patients with CAD. Appraisal of intravenous agents goes beyond the scope of this review.

ORAL ANTIPLATELET THERAPIES

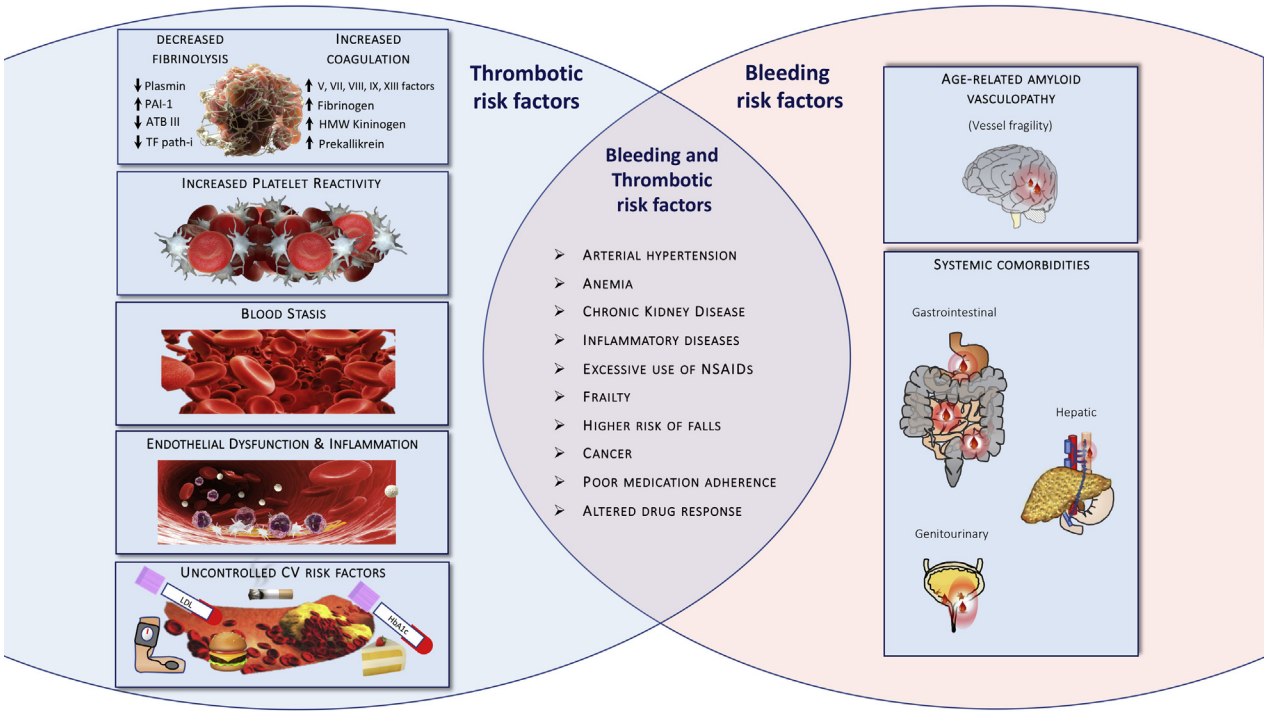
Aspirin and $P2Y_{12}$ inhibitors (clopidogrel, prasugrel, and ticagrelor) are the most commonly used antiplatelet agents. These agents can be used alone (i.e., single-antiplatelet therapy) or in combination (i.e., dual-antiplatelet therapy [DAPT]), such as in patients experiencing ACS or undergoing PCI (9). Details of these agents are provided later. Other antiplatelet agents with limited use, such as vorapaxar, or not approved for CAD prevention, such as cilostazol, are not discussed.

HIGHLIGHTS

- Risk stratification is key for patient-centered antithrombotics choice in the elderly.
- Bleeding risk should guide the choice of antithrombotic strategies in the elderly.
- Future studies are needed to assess novel antithrombotic strategies in the elderly.

ASPIRIN. Aspirin is an irreversible inhibitor of the platelet cyclooxygenase-1. Most recent evidence has shown aspirin to have either neutral or harmful effects in primary prevention, including 2 studies focused on older populations (10,11). In the JPPP (Japanese Primary Prevention Project) study, 14,464 subjects 60 to 85 years of age were randomized to no aspirin or aspirin 100 mg/day and showed no differences in the primary endpoint of cardiovascular death, stroke, or myocardial infarction and a doubling in the risk for major hemorrhage (10). The ASPREE (Aspirin in Reducing Events in the Elderly) study randomized 19,114 patients ≥70 years of age (≥65 years of age for black and Hispanic participants) to receive aspirin 100 mg or placebo daily and at a median of 4.7 years showed no differences in ischemic events (composite of fatal coronary heart disease, myocardial infarction, stroke, or hospitalization for heart failure) (11). Notably, major hemorrhages and mortality, due mostly to cancer, were significantly increased with aspirin (12). The trial also showed no reduction in the combined endpoint of dementia, death, or persistent physical disability (13). On the basis of these observations, updated guidelines do not recommend the use of aspirin for primary prevention in patients >70 years of age (14). However, aspirin represents the cornerstone of therapy for secondary prevention. A large meta-analysis conducted in patients 65 to 74 years of age showed that aspirin was associated with a 5-year absolute risk reduction in vascular events of approximately 10%, which was not offset by the absolute increase in nonfatal bleeding of only 0.5% (15). Although this meta-analysis focused on high-quality studies, bleeding events across these latter were largely underreported or not properly and prospectively collected, leading to an inaccurate assessment of the balance between aspirin-related benefits and risks. Moreover, those studies are outdated and included only a small number of patients >70 years of age, who

FIGURE 1 Risk Factors for Thrombotic and Bleeding Events in Elderly Patients



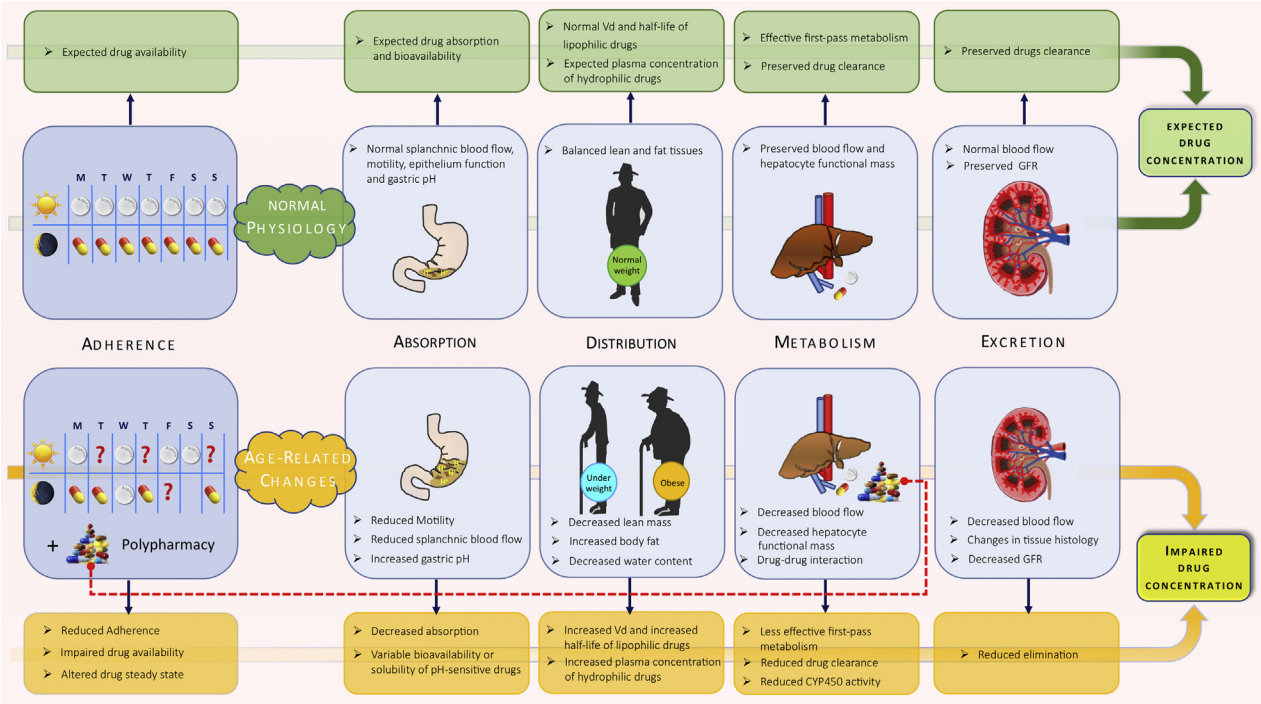
ATB = antithrombin; HbA1c = glycated hemoglobin; HMW = high-molecular weight; LDL = low-density lipoprotein; NSAID = nonsteroidal anti-inflammatory drug; PAI = plasminogen activator inhibitor; TF path-i = tissue factor pathway inhibitor.

are known to be more vulnerable to the gastrointestinal side effects of aspirin (16). These side effects have prompted the development of novel aspirin formulations (17). Moreover, studies challenging the role of aspirin for secondary prevention have been performed, as discussed later.

$P2Y_{12}$ RECEPTOR INHIBITORS. Clopidogrel is the most used $P2Y_{12}$ inhibitor and is recommended as an alternative in aspirin-intolerant patients (9). Clopidogrel is the only approved $P2Y_{12}$ inhibitor in patients with CCS undergoing PCI. Although clopidogrel is also approved for patients with ACS, prasugrel and ticagrelor are preferred in this setting (9). The evidence supporting the use of clopidogrel in patients with ACS derives from the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial, in which the addition of clopidogrel to aspirin versus aspirin alone was associated with a 20% relative risk reduction (RRR) on the 1-year ischemic endpoint at the expense of a 38% relative increase in major bleeding (18). Clopidogrel was more effective than placebo irrespective of age (**Table 1**). The benefits of adjunctive use of clopidogrel have been supported in a number of subsequent trials conducted in high-risk settings without signals for harm in elderly patients, making it a broadly used agent in this population who have an indication for DAPT. Despite its established efficacy, clopidogrel-induced antiplatelet effects are characterized by broad interpatient variability, with elderly subjects at increased risk for high platelet reactivity (HPR), a marker of thrombotic risk (19–21).

The effects of prasugrel and ticagrelor in elderly patients have been assessed in subgroup analyses of pivotal trials and dedicated age-specific studies (**Table 1**). In the TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis In Myocardial Infarction 38) trial, compared with clopidogrel, prasugrel was associated with a 19% RRR in the primary efficacy outcome in patients with ACS undergoing PCI at the expense of a 32% relative increase in major bleeding (22). Such excess in bleeding resulted in a neutral net clinical benefit in elderly patients (**Table 1**). On the basis of these findings, prasugrel is generally not recommended in patients ≥75 years of age. However, according to the

FIGURE 2 Age-Related Factors Affecting Pharmacokinetic and Pharmacodynamic Profiles of Antithrombotic Therapies



CYP = cytochrome P; GFR = glomerular filtration rate; Vd = volume of distribution.

U.S. Food and Drug Administration, prasugrel 10 mg may still be considered for older (≥75 years) high-risk (i.e., diabetes mellitus or prior myocardial infarction) patients, in the absence of contraindications (prior cerebrovascular event or active bleeding). The increased risk for bleeding among elderly patients can be attributed to increased exposure to the active metabolite of prasugrel 10 mg, which was greater with advanced age, although to a lesser extent compared with the effect of body weight, suggesting the need to reduce the maintenance dose to 5 mg also among elderly patients (23,24). Although prasugrel 5 mg provides more potent platelet inhibition compared with clopidogrel among elderly patients, the differences are small and do not translate into clinical benefits (25,26). In the subgroup of older patients of the TRILOGY ACS (Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes) study, prasugrel 5 mg versus clopidogrel 75 mg provided similar efficacy and safety among medically managed ACS patients (**Table 1**) (25). In the ELDERLY ACS II (Elderly Acute Coronary Syndrome 2) trial, which was interrupted after 1,443 patients (of the planned 2,000 patients) were enrolled because of futility for efficacy, there were no clinical differences with prasugrel 5 mg versus clopidogrel among invasively managed patients with ACS >74 years of age (**Table 1**) (26). In patients with ACS undergoing PCI ≥75 years of age (n = 877), the impact of prasugrel 5 or 10 mg or clopidogrel was tested using a platelet-function testing (PFT)-guided approach in the ANTARCTIC (Tailored Antiplatelet Therapy Versus Recommended Dose of Prasugrel) study (27). A PFT-guided dose or drug adjustment of prasugrel 5 mg versus treatment with prasugrel 5 mg without monitoring did not improve net clinical outcomes. This lack of benefit should be interpreted in light of the fact that PFT-guided therapy resulted in switching from prasugrel 5 mg to clopidogrel (because of low platelet reactivity) in 39% of patients and to prasugrel 10 mg (because of HPR) only in 4%. This mostly led to a neutral comparison between clopidogrel versus prasugrel 5 mg.

In the PLATO (Platelet Inhibition and Patient Outcomes) trial, ticagrelor compared with clopidogrel was associated with a 16% RRR in the primary ischemic endpoint in patients with ACS, irrespective of management (invasive or noninvasive) (28). Although there were no differences in the study-defined primary major bleeding endpoint, bleeding

TABLE 1 Age-Specific Data in Studies of Dual-Antiplatelet Therapy

Study	Population and Management	Follow-Up	Compared $P2Y_{12}$ Inhibitors*	Overall Patients and Age Subgroups	Primary Efficacy/Net Net Endpoint Rates HR (95% CI)	Bleeding Events Rates HR (95% CI)
CURE	NSTE-ACS PCI 21.2% CABG 16.5% CT 62.3%	1 yr	Clopidogrel vs. placebo	Overall, n = 12,562	CV death, MI, or stroke 9.3% vs. 11.4%; 0.80 (0.72–0.90)	Major bleeding 3.7% vs. 2.7%; 1.38 (1.13–1.67)
				Age ≤65 yrs, n = 6,354	5.4% vs. 7.6%; HR NA	Data NA
				Age >65 yrs, n = 6,208	13.3% vs. 15.3%; HR NA	Data NA
TRITON-TIMI 38	Invasively treated ACS PCI 99% CABG 1%	15 months	Prasugrel vs. clopidogrel	Overall, n = 13,608	CV death, MI, or stroke 9.9% vs. 12.1%; 0.76 (0.66–0.86)	TIMI major bleeding 2.4% vs. 1.8%; 1.32 (1.03–1.68)
				Age <65 yrs, n = 8,322	8.1% vs. 10.6%; HR NA	Bleeding data NA
				Age 65–74 yrs, n = 3,477	10.7% vs. 12.3%; HR NA	Bleeding data NA
				Age ≥75 yrs, n = 1,809	17.2% vs. 18.3 HR NA	Net clinical benefit: rates NA; 0.99 (0.81–1.21)†
TRILOGY ACS‡	Medically treated ACS	30 months	Prasugrel 5 mg vs. clopidogrel	Age ≥75 yrs, n = 2,083	CV death, MI, or stroke 35.6% vs. 35.8%; 1.03 (0.86–1.22)	TIMI major bleeding 4.1% vs. 3.4%; 1.09 (0.57–2.08)
ELDERLY ACS II	ACS and PCI with age ≥75 yrs	1 yr§	Prasugrel 5 mg vs. clopidogrel		Death, MI, stroke, rehospitalization for CV causes or bleeding	BARC type ≥2
				Age ≥75 yrs, n = 1,443	17% vs. 16.6%; 1.01 (0.78–1.30)	4.1% vs. 2.7%; 1.52 (0.85–3.16)
PLATO	Invasively and medically treated ACS PCI 61% CABG 45.5 CT 34.5%	1 yr	Ticagrelor vs. clopidogrel	Overall, n = 18,624	CV death, MI, or stroke 9.8% vs. 11.7%; 0.84 (0.77–0.92)	PLATO major bleeding 11.6% vs. 11.2%; 1.04 (0.95–1.13)
				Age <65 yrs, n = 10,643	7.2% vs. 8.5%; 0.85 (0.74–0.97)	9.5% vs. 9.5%; 1.00 (0.87–1.13)
				Age ≥65 yrs, n = 7,979	13.2% vs. 16.0%; 0.83 (0.74–0.94)	14.4% vs. 13.6%; 1.07 (0.95–1.22)
				Age <75 yrs, n = 15,744	8.6% vs. 10.4%; 0.84 (0.75–0.93)	11.2% vs. 10.8%; 1.04 (0.94–1.15)
				Age ≥75 yrs, n = 2,878	17.2% vs. 18.3%; 0.89 (0.74–1.08)	14.2% vs. 13.5%; 1.02 (0.82–1.27)
POPular AGE	NSTE-ACS with age ≥70 yrs PCI 47.3% CABG 16.5% CT 36.2%	1 yr	Clopidogrel vs. ticagrelor (95%)		Death, MI, stroke, or overall bleeding‖	PLATO major and minor bleeding¶
				Age ≥70 yrs, n = 1,443	28% vs. 32%; 0.82 (0.66–1.03)	18% vs. 24%; 0.71 (0.54–0.94)
ISAR-REACT 5‡	Invasively treated ACS PCI 84% CABG 2.1% CT 13.8%	1 yr	Prasugrel 5 mg vs. ticagrelor	Age ≥75 yrs, n = 1,099	Death, MI, or stroke 12.7% vs. 14.6%; 0.82 (0.60–1.14)	BARC type 3-5 8.1% vs. 10.6%; 0.72 (0.46–1.12)
BREMEN-STEMI Registry	STEMI with age ≥75 yrs PCI 100%	1 yr	Ticagrelor vs. clopidogrel	Age ≥75 yrs, n = 1,087	Death, MI, or stroke 25.5% vs. 32.4%; adjusted HR: 0.69 (0.49–0.97)	Significant bleeding 5.1% vs. 4.9%; adjusted HR: 1.08 (0.49–2.37)
SWEDEHEART registry	MI with age ≥80 yrs PCI 58.3%	1 yr	Ticagrelor vs. clopidogrel	Age ≥80 yrs, n = 14,005	Death, MI, or stroke 18.7% vs. 32.8%; adjusted HR: 0.97 (0.88–1.06)	Readmission for bleeding 6.90% vs. 4.86%; adjusted HR: 1.48 (1.25–1.76)

All p values for interaction were not significant. *Where not specified, the dose of the $P2Y_{12}$ inhibitor refers to the standard one (75 mg for clopidogrel, 10 mg for prasugrel, and 90 mg for ticagrelor). †Endpoint defined as death, MI, stroke, or major bleeding that was available only for age subgroup ≥75 years. ‡The younger subgroups of these two studies were not reported, because patients were treated with prasugrel 10 mg and thus cannot be comparable with the older one in which patients were treated with prasugrel 5 mg. §Follow-up range 3 to 13 months. ‖p value for noninferiority = 0.025. ¶Fatal bleeding was 0% with clopidogrel and 1.0% with ticagrelor/prasugrel (p = 0.03).

ACS = acute coronary syndrome(s); BARC = Bleeding Academic Research Consortium; CABG = coronary artery bypass grafting; CI = confidence interval; CT = conservative treatment; CURE = Clopidogrel in Unstable Angina to Prevent Recurrent Events; CV = cardiovascular; ELDERLY ACS II = Elderly Acute Coronary Syndrome 2; HR = hazard ratio; ISAR-REACT 5 = Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 5; MI = myocardial infarction; NA = not available; NSTE-ACS = non-ST-segment elevation acute coronary syndrome; PCI = percutaneous coronary intervention; PLATO = Platelet Inhibition and Patient Outcomes; POPular AGE = Ticagrelor or Prasugrel Versus Clopidogrel in Elderly Patients With an Acute Coronary Syndrome and a High Bleeding Risk: Optimization of Antiplatelet Treatment in High-Risk Elderly; STEMI = ST-segment elevation myocardial infarction; SWEDEHEART = Swedish Web System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies; TIMI = Thrombolysis In Myocardial Infarction; TRILOGY ACS = Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes; TRITON-TIMI 38 = Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis In Myocardial Infarction 38.

not related to coronary artery bypass grafting was higher with ticagrelor. Although bleeding events increased with age, they were not significantly increased in ticagrelor- versus clopidogrel-treated patients across age subgroups (**Table 1**) (29). Accordingly, use of ticagrelor 90 mg twice daily is recommended after ACS, with no specific age-related recommendations (9). More contemporary evidence with potent $P2Y_{12}$ inhibitors (mostly ticagrelor) versus clopidogrel in elderly patients (>70 years of age) derives from the POPular AGE (Ticagrelor or Prasugrel Versus Clopidogrel in Elderly Patients With an Acute Coronary Syndrome and a High Bleeding Risk: Optimization of Antiplatelet Treatment in High-Risk Elderly) trial, in which clopidogrel significantly reduced net clinical outcomes due to decreased bleeding without differences in ischemic events, although the trial was not powered to detect a difference in efficacy endpoints (**Table 1**) (30). Of note, in the POPular AGE trial, premature discontinuation or switching of the study drug occurred in 47% of patients randomized to ticagrelor, compared with 22% of those randomized to clopidogrel, which could have potentially diminished the beneficial effects of ticagrelor. However, the most important reasons for discontinuation of ticagrelor, including dyspnea, concomitant use of OACs, and bleeding, reflect the high prevalence of issues that may interfere with complying with ticagrelor therapy in elderly patients.

In the Bremen STEMI Registry, ticagrelor was associated with decreased ischemic events and no significant increase in bleeding (31). Differently, in the SWEDEHEART (Swedish Web System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies) registry, ticagrelor provided similar efficacy to clopidogrel but increased bleeding and mortality (32). Although adjustments were performed, several unmeasured variables could have affected these outcomes (33,34). Finally, in the subgroup of elderly (≥75 years of age) or low-weight (<60 kg) patients of the ISAR-REACT 5 (Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 5) trial, a reduced dose of prasugrel compared with the standard dose of ticagrelor was associated with maintained anti-ischemic efficacy while protecting these patients against the excess risk for bleeding (**Table 1**) (35).

The aforementioned studies evaluated a DAPT regimen up to 1 year after the index event. However, the persistent risk for ischemic recurrences has prompted investigations evaluating extended DAPT (**Table 2**) (36–38). In the DAPT (Dual Antiplatelet Therapy) trial, patients undergoing PCI were randomized after 1 year to maintain, in adjunct to aspirin, a $P2Y_{12}$ inhibitor (clopidogrel, 65%; prasugrel, 35%) for 30 months versus aspirin only (36). Prolonged DAPT provided a 29% RRR in overall ischemic events and a 71% RRR in stent thrombosis, at the expense of 61% relative increase in bleeding. These results were consistent in age-stratified subgroups, although the efficacy benefit of prolonged DAPT was attenuated, and bleeding rates increased with age (**Table 2**). These findings led to an unfavorable impact of age on the DAPT score, which was developed to identify patients who benefited from extended DAPT (39).

In patients with prior myocardial infarction (1 to 3 years from the index event), the PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis In Myocardial Infarction 54) trial showed that the addition of ticagrelor 90 mg or 60 mg to aspirin was associated with 15% and 16% RRR, respectively, on the 3-year primary ischemic outcome at the expense of a 132% increase in bleeding (37). These results were consistent across age subgroups (**Table 2**). However, ticagrelor 60 mg had a better safety profile and accordingly this regimen was approved for long-term secondary prevention. In the THEMIS (The Effect of Ticagrelor on Health Outcomes in Diabetes Mellitus Patients Intervention Study) trial, the addition of ticagrelor 60 mg to aspirin in patients with diabetes mellitus and stable CAD, but without prior major cardiovascular event (myocardial infarction or stroke) was associated with a 10% RRR on the primary ischemic outcome, at expense of a 2.3-fold increase in major bleeding (38). Despite no significant interaction with age, the primary ischemic endpoint was not significantly reduced with ticagrelor among patients ≥75 years of age and bleeding was increased across all age subgroups (**Table 2**).

OAC THERAPY

Beyond their well-established role for the prevention of venous and arterial thromboembolism, OACs have been tested for preventing ischemic recurrences in patients with CAD (40). The use of a vitamin K antagonist (VKA) in combination with aspirin showed to reduce ischemic recurrences in patients with ACS, at the expense of increased bleeding (41). The introduction of non-VKA OACs (direct OACs), characterized by a more favorable clinical profile compared with VKAs in patients with AF and venous thromboembolism, renewed interest in the role of OACs in combination with antiplatelet therapy in patients with CAD. Several direct OACs have been

TABLE 2 Age-Specific Data in Studies of Extended Dual-Antiplatelet Therapy

Study	Population	Follow-Up	DAPT vs. Aspirin	Overall Patients and Age Subgroups	DAPT vs. Aspirin: Primary Efficacy Endpoint Rates HR (95% CI)	DAPT vs. Aspirin: Bleeding Events Rates HR (95% CI)
DAPT	1 yr after PCI and DAPT (without prior ischemic or bleeding)	30 months	Clopidogrel or prasugrel plus aspirin vs. aspirin + placebo		Death, MI, or stroke	GUSTO moderate/severe
				Overall, n = 9,961	4.3% vs. 5.9%; 0.71 (0.59–0.85)	2.5% vs. 1.6%; 1.61 (1.21–2.16)
				Age <75 yrs, n = 8,929	4.0% vs. 5.8%; 0.69 (0.57–0.83)	2.3% vs. 1.3%; 1.78 (1.29–2.47)
				Age ≥75 yrs, n = 1,032	6.8% vs. 7.1%; 0.95 (0.59–1.52)	3.7% vs. 3.6%; 1.03 (0.54–1.98)
PEGASUS-TIMI 54*	Prior MI (>1–3 yrs)†	3 yrs	Ticagrelor 60 mg plus aspirin vs. aspirin + placebo		CV death, MI, or stroke	TIMI major bleeding
				Overall, n = 21,162	7.77% vs. 9.04%; 0.84 (0.74–0.95)	2.30% vs. 1.06%; 2.32 (1.68–3.21)
				Age <75 yrs, n = 18,079	7.23% vs. 8.27%; 0.86 (0.75–0.98)	2.05% vs. 0.96%; 2.30 (1.60–3.32)
				Age ≥75 yrs, n = 3,083	11.0% vs. 13.5%; 0.77 (0.59–1.01)	4.11% vs. 1.68%; 2.50 (1.25–4.97)
THEMIS	DM with stable CAD	54 months	Ticagrelor 60 mg plus aspirin vs. aspirin + placebo		CV death, MI, or stroke	TIMI major bleeding
				Overall, n = 19,220	7.7% vs. 8.5%; 0.90 (0.81–0.99)	2.2% vs. 1.0%; 2.32 (1.82–2.94)
				Age <65 yrs, n = 7,934	6.1% vs. 7.3%; 0.83 (0.70–0.98)	2.0% vs. 0.9%; 2.33 (1.58–3.43)
				Age 65–75 yrs, n = 8,890	7.4% vs. 8.4%; 0.89 (0.77–1.03)	2.3% vs. 1.0%; 2.49 (1.75–3.53)
				Age >75 yrs, n = 2,396	13.6% vs. 13.1%; 1.07 (0.86–1.33)	2.2% vs. 1.4%; 1.89 (1.03–3.49)

All p values for interaction were not significant. *Outcomes refer to the comparison of ticagrelor 60 mg versus placebo. †One of the following additional high-risk factors was required for enrolment: age ≥65 years, diabetes mellitus requiring medication, recurrent MI, multivessel CAD, or estimated creatinine clearance <60 ml/min.

CAD = coronary artery disease; DAPT = dual-antiplatelet therapy; DM = diabetes mellitus; GUSTO = Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries; PEGASUS-TIMI 54 = Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis In Myocardial Infarction 54; THEMIS = The Effect of Ticagrelor on Health Outcomes in Diabetes Mellitus Patients Intervention Study; other abbreviations as in Table 1.

tested, but only one (i.e., rivaroxaban) met its primary endpoint in phase III clinical testing (42).

In the ATLAS ACS-2-TIMI 51 (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects With Acute Coronary Syndrome-Thrombolysis In Myocardial Infarction 51) trial, rivaroxaban 5 or 2.5 mg twice daily versus placebo reduced ischemic outcomes at the expense of increased major bleeding in patients with ACS treated mostly with clopidogrel-based DAPT (42). Although trial results were consistent across age subgroups, the increase in bleeding with rivaroxaban was greater in patients ≥65 years of age (Table 3). As the safety profile was best with rivaroxaban 2.5 mg, this was the dose approved for ACS by several drug-regulating agencies, but not the Food and Drug Administration.

In the COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial patients with stable cardiovascular disease, including CAD or peripheral artery disease, were randomized to rivaroxaban 2.5 mg twice daily plus aspirin, also known as dual-pathway inhibition, rivaroxaban 5.0 mg twice daily alone or aspirin 100 mg alone (43). A reduction of the primary efficacy endpoint with dual-pathway inhibition occurred at the expense of increased bleeding (Table 3). The primary efficacy outcome was not significantly lower with rivaroxaban 5.0 mg. Despite no significant interaction with age, among patients ≥75 years of age, the magnitude of benefit with dual-pathway inhibition was reduced, and the relative increase in major bleeding was higher (Table 3). On the basis of the COMPASS trial, rivaroxaban 2.5 mg twice daily was approved for patients with chronic CAD or peripheral artery disease by most regulatory agencies without age-specific recommendations.

BLEEDING REDUCTION STRATEGIES

The adverse prognosis of bleeding has fueled interest in defining strategies to reduce this risk while preserving efficacy (44). Bleeding reduction strategies have been particularly investigated in settings requiring the use of DAPT. Beyond selecting a $P2Y_{12}$ inhibitor according to its potency, additional strategies include 1) shortening DAPT duration by dropping the $P2Y_{12}$ inhibitor and continuing aspirin; 2) de-escalation from a more to less potent $P2Y_{12}$ inhibitor;

TABLE 3 Age-Specific Data in Studies of Dual-Pathway Inhibition

Study	Population	Follow-Up	DPI vs. Antiplatelet	Overall Patients and Age Subgroups	Primary Efficacy Endpoint Rates HR (95% CI)	Bleeding Events Rates HR (95% CI)
ATLAS ACS-2–TIMI 51*	Stabilized ACS	2 yrs	Rivaroxaban 5 or 2.5 mg plus aspirin or DAPT† (93%) vs. aspirin or DAPT† (93%) + placebo		CV death, MI, or stroke	TIMI major bleeding‡
				Overall, n = 15,526	8.9% vs. 10.7%; 0.84 (0.74–0.96)	2.1% vs. 0.8%; 3.96 (2.46–6.38)
				Age <65 yrs, n = 9,735	5.1% vs. 6.2%; 0.83 (0.70–0.99)	1.3% vs. 0.4%; 3.45 (1.93–6.19)
				Age ≥65 yrs, n = 5,607	7.9% vs. 9.5%; 0.84 (0.70–1.01)	1.6% vs. 0.3%; 5.03 (2.17–11.62)
COMPASS*	Stable CV disease	3 yrs	Rivaroxaban 2.5 mg plus aspirin vs. aspirin + placebo		CV death, stroke, or MI	TIMI major bleeding
				Overall, n = 18,278	4.1% vs. 5.4%; 0.76 (0.66–0.86)	3.1% vs. 1.9%; 1.70 (1.40–2.05)
				Age <65 yrs, n = 4,334	3.7% vs. 5.8%; 0.63 (0.48–0.84)	1.4% vs. 1.2%; 1.18 (0.70–1.97)
				Age 65–74 yrs, n = 10,123	3.5% vs. 4.7%; 0.74 (0.61–0.90)	3.1% vs. 1.9%; 1.63 (1.26–2.10)
				Age ≥75 yrs, n = 3,821	6.3% vs. 7.0%; 0.89 (0.69–1.14)	5.2% vs. 2.5%; 2.12 (1.50–3.00)

All p values for interaction were not significant. *Numbers refer to the comparison between the combination of rivaroxaban 2.5 mg versus aspirin alone. †With clopidogrel or ticlopidine. ‡Not related to coronary artery bypass grafting.

ATLAS ACS-2–TIMI 51 = Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects With Acute Coronary Syndrome–Thrombolysis In Myocardial Infarction 51; COMPASS = Cardiovascular Outcomes for People Using Anticoagulation Strategies; DPI = dual-pathway inhibition; other abbreviations as in Tables 1 and 2.

and 3) dropping aspirin from DAPT and maintaining $P2Y_{12}$ inhibitor monotherapy.

SHORTENING DAPT DURATION. The introduction of novel drug-eluting stents with improved safety profile has allowed testing abbreviated durations of DAPT (45). Most evidence on different DAPT durations in elderly patients derives from subgroup analyses of randomized clinical trials, which have consistently shown no significant differences in net clinical events between shorter versus longer DAPT regimens (46). A patient-level meta-analysis of randomized clinical trials assessed the impact of age on outcomes of different DAPT durations in patients undergoing PCI with drug-eluting stents (47). Short (3 to 6 months) versus standard (12 months) DAPT was compared between patients <65 years of age (n = 6,152) and those ≥65 years of age (n = 5,319). In the elderly cohort subgroup, short DAPT was noninferior to standard DAPT on rates of myocardial infarction, stent thrombosis, and stroke and significantly reduced major bleeding. On the contrary, in patients <65 years of age, short DAPT was associated with higher ischemic event rates without significant reduction in major bleeding. Although no differences in efficacy were observed between short and standard DAPT duration, extended DAPT (>12 months) was associated with reduced myocardial infarction and increased bleeding (45). However, elderly patients are not ideal candidates to achieve the optimal risk-benefit balance with extended DAPT (39,48).

$P2Y_{12}$ INHIBITOR DE-ESCALATION. The observation that the greatest anti-ischemic benefits of more potent $P2Y_{12}$ inhibitors are seen within 30 days after an acute event, while bleeding accrues during longer term treatment, has set the rationale for switching from a more to a less potent $P2Y_{12}$ inhibitor following the early ACS phase (20,49). Studies of $P2Y_{12}$ de-escalation that have reported age-stratified outcomes are listed in **Table 4** (50–53). The HOST-REDUCE-POLYTECH-ACS (Harmonizing Optimal Strategy for Treatment of Coronary Artery Diseases Trial—Comparison of Reduction of Prasugrel Dose & Polymer Technology in ACS Patients) trial compared a de-escalation from prasugrel 10 to 5 mg at 1 month after ACS versus conventional treatment with 1-year prasugrel 10 mg and showed that de-escalation reduced bleeding, leading to lower net clinical events (50). These results were consistent irrespective of age (**Table 4**). Despite the encouraging outcomes with de-escalation, this strategy has raised concerns when the transition in therapy occurs toward clopidogrel in light of the considerable number of patients who may have HPR. This has fueled interest in deescalating $P2Y_{12}$ inhibiting therapy after excluding patients with HPR (using PFT) or at risk for developing HPR (using genetic testing) (20). In the TROPICAL-ACS (Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment for Acute Coronary Syndromes) trial, the net clinical benefit of a PFT-guided de-escalation was noninferior to conventional non-guided 12-month prasugrel treatment (**Table 4**) (51).

TABLE 4 Age-Specific Data in Studies of $P2Y_{12}$ Inhibitor De-Escalation

Study	Population	Follow-Up	De-Escalation Strategy	Standard DAPT Treatment	Overall Patients and Age Subgroups	Primary Endpoint Rates De-Escalation vs. Standard DAPT HR (95% CI)	
HOST-REDUCE-POLYTECH-ACS	ACS and PCI	1 yr	Switching from prasugrel 10 mg to prasugrel 5 mg at 1 month	Aspirin plus prasugrel 10 mg for 1 yr		CV death, MI stroke, ST, repeat revascularization, or BARC type ≥2	
					Overall, n = 2,338	7.2% vs. 10.1%; 0.70 (0.52–0.92)	
					Age <65 yrs, n = 1,635	6.5% vs. 8.9%; 0.73 (0.51–1.04)	
					Age ≥65 yrs, n = 703	8.1% vs. 12.3%; 0.65 (0.40–1.04)	
TROPICAL-ACS	ACS and PCI	1 yr	1 week prasugrel followed by 1 week clopidogrel and PFT-guided therapy with clopidogrel or prasugrel thereafter	Aspirin plus prasugrel 10 mg for 1 yr		CV death, MI, stroke, or BARC type ≥2	
					Overall, n = 2,610	7% vs. 9%; 0.81 (0.62–1.06)	
					Age ≤70 yrs, n = 2,240	5.9% vs. 8.3%; 0.70 (0.51–0.96)	
					Age >70 yrs, n = 370	15.5% vs. 13.6%; 1.17 (0.69–2.01)	
POPular Genetics	ACS and PCI	1 yr	Carriers of CYP2C19*2 or CYP2C19*3 loss-of-function alleles received ticagrelor or prasugrel, and noncarriers received clopidogrel	Aspirin plus prasugrel or ticagrelor for 1 yr		Death, MI, stroke, ST or PLATO major bleeding	PLATO major or minor bleeding
					Overall, n = 2,488	5.1% vs. 5.9%; 0.87 (0.62–1.21)	9.8% vs. 12.5%; 0.78 (0.61–0.98)
					Age <75 yrs, n = 2,125	4.1% vs. 4.9%; 0.82 (0.55–1.23)	8.7% vs. 11.4%; 0.76 (0.58–1.04)
					Age ≥75 yrs, n = 363	10.6% vs. 11.4%; 0.94 (0.51–1.75)	16.0% vs. 19.4%; 0.80 (0.49–1.30)

All p values for interaction were not significant.

HOST-REDUCE-POLYTECH-ACS = Harmonizing Optimal Strategy for Treatment of Coronary Artery Diseases Trial—Comparison of Reduction of Prasugrel Dose & Polymer Technology in ACS Patients; PFT = platelet function testing; ST = stent thrombosis; TROPICAL-ACS = Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment for Acute Coronary Syndromes; other abbreviations as in Table 1.

An age-specific analysis showed that a PFT-guided de-escalation was associated with reduced net clinical outcomes in patients <70 years of age, while no net clinical benefit was observed in older patients (52) (**Table 4**). However, the sample size of elderly patients was limited (n = 370 [14% of the trial population]), and those >80 years of age were excluded. In the POPular GENETICS trial, cytochrome P450 2C19 genotype-guided $P2Y_{12}$ inhibitor selection was associated with decreased bleeding, especially minor, and similar ischemic outcomes compared with standard 12-month prasugrel or ticagrelor treatment, resulting in a noninferior net endpoint (53). These findings were consistent across age-stratified subgroups (**Table 4**).

ASPIRIN-FREE APPROACHES. Antithrombotic regimens have been developed using aspirin as a background therapy, hence obscuring an understanding of the relative effects of adjunctive therapies (54). Of note, aspirin minimally affects antithrombotic effects when more potent antithrombotic drugs are being used, yet it may still contribute to bleeding in light of its gastrointestinal toxicity (54). These considerations have prompted investigations evaluating aspirin-free antithrombotic approaches in patients undergoing PCI (54). The strategy of omitting aspirin was first studied in patients with AF undergoing PCI, consistently showing that the combination of OAC with DAPT, also known as triple-antithrombotic therapy, increases the risk for bleeding, especially in older patients (55). Several randomized clinical trials have shown that limiting the use of aspirin to the peri-PCI phase and maintaining double-antithrombotic therapy (DAT) with an OAC, preferably a direct OAC, and a $P2Y_{12}$ inhibitor, preferably clopidogrel, represents the strategy of choice given to reduce bleeding without compromising efficacy (55). Available results from these randomized clinical trials have consistently shown more favorable outcomes with aspirin-free DAT versus triple-antithrombotic therapy across age subgroups with all direct OAC (**Table 5**) (56–59). The only exception was with dabigatran 110 mg-based DAT, which was associated with increased thromboembolic events among older patients compared with VKA-based triple-antithrombotic therapy (60). On the basis of these observations, a direct OAC should be used at the stroke prevention dosing regimen, unless specifically tested in an randomized clinical trial (i.e., rivaroxaban) (61,62). It is important to note that many elderly patients may have criteria for adjusted dosing (**Table 6**). Several studies have assessed aspirin-free

TABLE 5 Age-Specific Data in Studies Assessing Aspirin-Free Approaches in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention Treated With Oral Anticoagulation

Study	Population	Follow-Up	DAT (Aspirin-Free) vs. TAT	Overall Patients and Age Subgroups	Ischemic Events Rates HR (95% CI)*	Bleeding Events Rates HR (95% CI)*
PIONEER AF-PCI†	AF and PCI	1 yr	Rivaroxaban 15 mg plus SAPT for 12 months vs. warfarin plus DAPT for 1, 6, or 12 months		CV death, MI, or stroke	Clinically relevant bleeding
				Overall, n = 1,415	6.5% vs. 6.0%; 1.08 (0.69–1.68)	16.8% vs. 26.7%; 0.59 (0.47–0.76)
				Age <75 yrs, n = 931	8.1% vs. 4.8%; 1.65 (0.74–3.68)	14.8% vs. 24.6%; 0.56 (0.41–0.77)
				Age ≥75 yrs, n = 484	5.6% vs. 6.5%; 0.86 (0.49–1.50)	20.6% vs. 31.4%; 0.62 (0.42–0.90)
RE-DUAL PCI	AF and PCI	1 yr	Dabigatran 110 or 150 mg plus SAPT for 12 months vs. warfarin plus DAPT for 1 or 3 months		Death, MI, stroke, SE, or unplanned revascularization	Major or clinically relevant nonmajor bleeding
				Overall, n = 2,725	For dabigatran 110: 15.2% vs. 13.4%; 1.13 (0.90–1.43)	For dabigatran 110: 15.4% vs. 26.9%; 0.52 (0.42–0.63)
					For dabigatran 150: 11.8% vs. 12.8%; 0.89 (0.67–1.19)	For dabigatran 150: 20.2% vs. 25.7%; 0.72 (0.58–0.88)
				Age <75 yrs, n = 1,699	For dabigatran 110: 13.7% vs. 14.5%; 0.90 (0.66–1.23)	For dabigatran 110: 11.9% vs. 26.1%; 0.40 (0.30–0.54)
					For dabigatran 150: 11.7% vs. 14.2%; 0.79 (0.57–1.09)	For dabigatran 150: 17.0% vs. 26.4%; 0.57 (0.44–0.74)
				Age ≥75 yrs, n = 1,026	For dabigatran 110: 17.3% vs. 11.7%; 1.54 (1.07–2.22)	For dabigatran 110: 20.1% vs. 28.0%; 0.67 (0.51–0.89)
					For dabigatran 150: 12.1% vs. 9.1%; 1.34 (0.73–2.44)	For dabigatran 150: 29.1% vs. 23.6%; 1.21 (0.83–1.77)
AUGUSTUS	AF and PCI	6 months	Apixaban or VKA plus SAPT plus aspirin-matched placebo for 6 months vs. apixaban or VKA plus DAPT for 6 months		Death, MI, stroke, ST, or urgent revascularization,‡ TAT vs. DAT	Major or clinically relevant nonmajor bleeding,‡ TAT vs. DAT
				Overall, n = 4,614	6.5% vs. 7.3%; 0.89 (0.71–1.11)	16.1% vs. 9.0%; 1.89 (1.59–2.24)
				Age <65 yrs, n = 1,267	Rates NA; 0.89 (0.55–1.42)	Rates NA; 1.65 (1.13–2.40)
				Age 65-79 yrs, n = 2,644	Rates NA; 0.94 (0.69–1.26)	Rates NA; 2.00 (1.60–2.50)
				Age ≥80 yrs, n = 703	Rates NA; 0.76 (0.48–1.19)	Rates NA; 1.83 (1.26–2.66)
ENTRUST-AF PCI	AF and PCI	1 yr	Edoxaban plus SAPT for 12 months vs. VKA plus DAPT for 1–12 months		CV death, MI, stroke, SE or ST‡	Major or clinically relevant nonmajor bleeding‡
				Overall, n = 1,506	7% vs. 6%; 1.06 (0.71–1.69)	17% vs. 20%; 0.83 (0.65–1.05)
				Age <65 yrs, n = 428	NA	13.7% vs. 18.7%; HR NA
				Age 65-74 yrs, n = 572	NA	19.9% vs. 23.2%; HR NA
				Age ≥75 yrs, n = 506	NA	29.1% vs. 35.0%; HR NA

All p values for interaction were not significant, except for ischemic events and bleeding events with dabigatran 110 mg and only for bleeding with dabigatran 150 mg. *Event rates and risk estimates are reported for DAT versus TAT in all studies except for the AUGUSTUS trial, in which they were reported for TAT versus DAT. †Numbers refer to the comparison between rivaroxaban 15 mg and warfarin treatment arms; results of the rivaroxaban 2.5 mg arm are not reported, as this dose is not approved for atrial fibrillation. ‡Event rates and risk estimates across age subgroups were not available for AUGUSTUS and ENTRUST-AF PCI, respectively.

AF = atrial fibrillation; AUGUSTUS = An Open- Label, 2Â~2 Factorial, Randomized, Controlled, Clinical Trial to Evaluate the Safety of Apixaban vs Vitamin K Antagonist and Aspirin vs Aspirin Placebo in Patients With Atrial Fibrillation and Acute Coronary Syndrome and/or Percutaneous Coronary Intervention; DAT = dual-antithrombotic therapy; ENTRUST-AF PCI = Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; PIONEER AF-PCI = Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention; RE-DUAL PCI = Evaluation of Dual Therapy With Dabigatran vs. Triple Therapy With Warfarin in Patients With AF That Undergo a PCI With Stenting; SAPT = single-antiplatelet therapy; SE = systemic embolism; VKA = vitamin K antagonist; other abbreviations as in Tables 1, 2, and 4.

antiplatelet strategies in patients undergoing PCI without a concomitant indication for chronic therapy with OAC (63-68). Overall, with the exception of GLOBAL LEADERS, all studies have shown that $P2Y_{12}$ inhibitor monotherapy after 1- or 3-month DAPT has been associated with reduced bleeding and similar ischemic events compared with standard 12-month DAPT (Figure 3). Consistent results were observed across age subgroups, although net clinical benefit with an aspirin-free approach appears to be enhanced among elderly subgroups in most studies (Figure 3). Main reasons for why bleeding was not reduced in GLOBAL LEADERS may include a likely underestimation of investigator-reported events that lacked of adjudication and the assessment of a heterogenous population comprising stable CAD and ACS (treated with clopidogrel or ticagrelor, in the conventional DAPT arm, respectively). In the GLASSY (GLOBAL LEADERS Adjudication Sub-Study) analysis, Bleeding Academic Research Consortium-defined major bleeding tended to occur more frequently as assessed by a central adjudication process, although event rates were similar in the $P2Y_{12}$ inhibitor monotherapy versus the DAPT conventional arm (69). However, major bleeding tended to be lower with ticagrelor monotherapy among patients with ACS (70).

PRACTICAL RECOMMENDATIONS

Older patients with CAD have an increased risk for bleeding that can counterbalance the ischemic benefit of antithrombotic therapies. As bleeding is associated

TABLE 6 Approved Doses of Direct Oral Anticoagulant for Stroke Prevention in Atrial Fibrillation

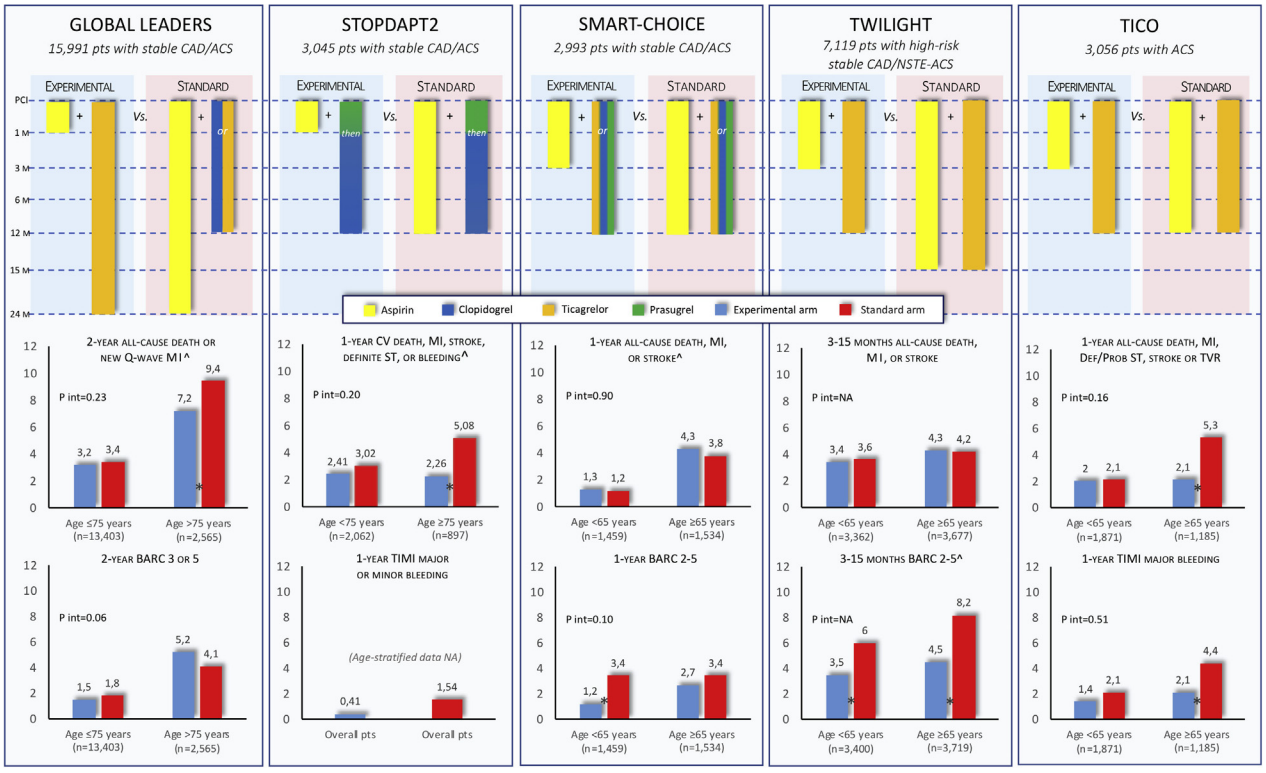
Dose Regimens	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Standard dose	In Europe: 150 (only if age <80 yrs and low bleeding risk) or 110 mg In United States: 150 mg In Japan: 150 (only if age <70 years and low bleeding risk) or 110 mg	20 mg once daily	5 mg twice daily	60 mg once daily if creatinine clearance 51–90 ml/min
Adjusted dose	In United States: 75 mg twice daily if creatinine clearance 15–30 ml/min	15 mg once daily if creatinine clearance 15–50 mL/min	2.5 mg twice daily if any two of the following: age ≥80 yrs, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dl	30 mg once daily if creatinine clearance 15–50 ml/min
Recommended dose approved in AF PCI	Same standard dose approved for stroke prevention in AF	15 mg once daily	Same standard and adjusted doses approved for stroke prevention in AF	Same standard and adjusted doses approved for stroke prevention in AF

Abbreviations as in Tables 1 and 5.

with increased mortality, all efforts should be made to maintain a favorable risk-benefit trade-off with the use of antithrombotic agents (44). A dynamic risk assessment should guide antithrombotic management, with guideline recommendations indicating that bleeding more than ischemic risk should inform decision making (9,62). Several strategies aimed at minimizing bleeding while maintaining efficacy can be considered (**Central Illustration**). General measures to mitigate bleeding include the use of radial access in patients undergoing PCI, close follow-up, use of proton pump inhibitors, avoidance of nonsteroidal anti-inflammatory drugs, and control of concomitant risk factors. In particular, it has been recently shown that routine use of proton pump inhibitors in patients receiving low-dose anticoagulation and/or aspirin for stable CAD reduce bleeding from gastroduodenal lesions (71).

From an antiplatelet standpoint, clopidogrel is the only recommended agent in patients with CCS undergoing PCI (9). In patients experiencing ACS, the first decision-making step includes the choice between potent $P2Y_{12}$ inhibitors and clopidogrel. Prasugrel 10 mg is generally not recommended among elderly patients, so the decision should be between ticagrelor and clopidogrel or prasugrel 5 mg. The increased bleeding risk with ticagrelor versus clopidogrel supports careful risk stratification among the heterogeneous elderly population. As bleeding causes are multifactorial and variable among elderly patients, an individual risk assessment should be performed in this population. This should take into consideration quantitative (i.e., risk scores) and qualitative (i.e., functional, social, and cognitive status) metrics (33). Indeed, it has been shown that risk scores are only moderately accurate in predicting bleeding risk in elderly patients >74 years of age (n = 1,883), with PRECISE-DAPT having better accuracy than the PARIS risk score (72). Of note, age ≥75 years by itself without other coexisting comorbidities is not considered a major bleeding risk factor in the recent Academic Research Consortium for High Bleeding Risk criteria (73). However, several comorbid conditions are commonly present in elderly patients, likely explaining the observation that patients ≥75 years of age without other concomitant minor Academic Research Consortium for High Bleeding Risk (HBR) criteria had an actual risk for bleeding above the Bleeding Academic Research Consortium type 3 or 5 4% threshold used to define HBR status according to Academic Research Consortium criterion (74). These data would suggest that probably age as a continuum, instead of a cutoff criterion, in combination with multiple variables could be considered for risk stratification (75). On the basis of the relative efficacy and safety of ticagrelor versus clopidogrel observed in an elderly population with myocardial infarction from a large registry, it has been hypothesized that ticagrelor might still provide a reduction in net events for baseline bleeding risk <4% (32,34). Thus, although dedicated studies on more homogenous bleeding risk-stratified patients are needed, ticagrelor can be selected in nonfrail, non-HBR elderly patients if no contraindications and other clinical factors associated with bleeding not included in scores are present. Although data are limited, prasugrel 5 mg resulted in numerically lower bleeding and similar efficacy compared with standard-dose ticagrelor (35). In patients in whom ticagrelor is chosen, dropping aspirin after a brief period of DAPT (e.g., 3 months) is a reasonable option, as now endorsed in recent

FIGURE 3 Design and Age-Specific Results of Randomized Studies Comparing $P2Y_{12}$ Monotherapy (Experimental Arm) Versus Standard 12-Month Dual Antiplatelet Therapy

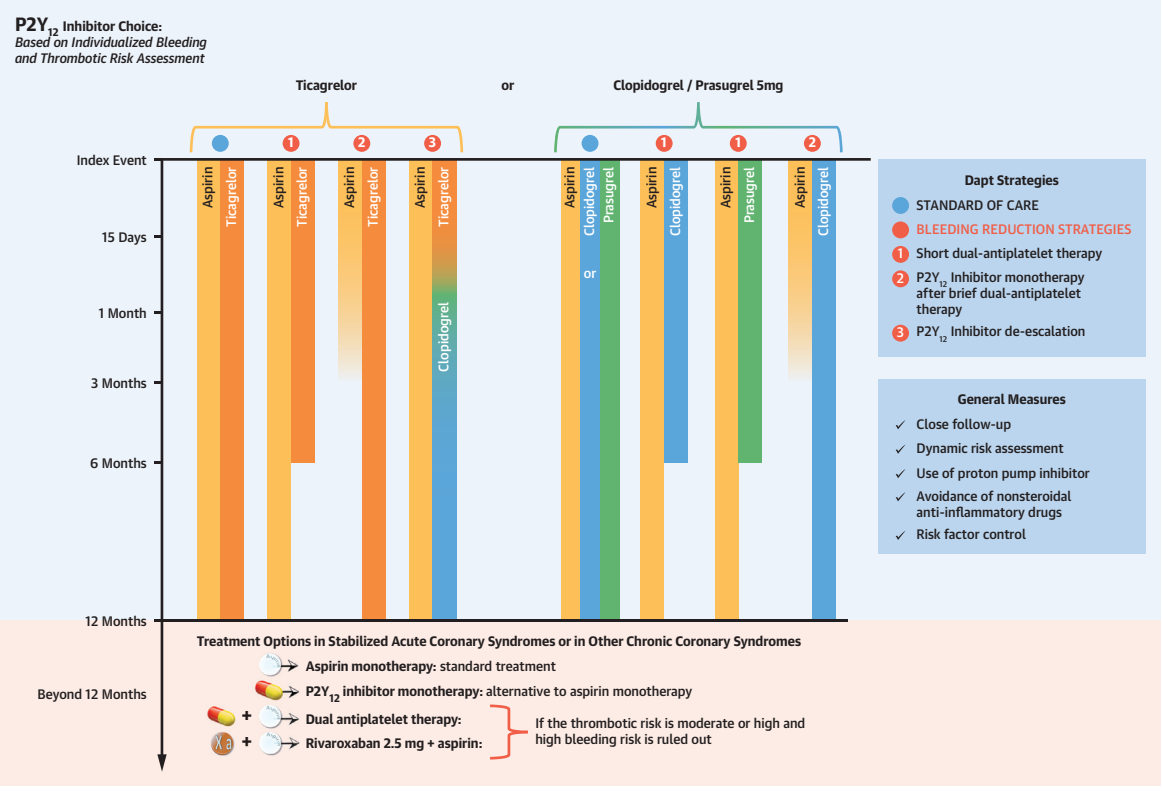


*Statistically significant difference. ^Primary endpoint. ACS = acute coronary syndrome(s); BARC = Bleeding Academic Research Consortium; CAD = coronary artery disease; CV = cardiovascular; Def/Prob = definite or probable; GLOBAL LEADERS = A Clinical Study Comparing Two Forms of Anti-platelet Therapy After Stent Implantation; MI = myocardial infarction; NA = not available; NSTE-ACS = non-ST-segment elevation acute coronary syndrome; SMART-CHOICE = In the Smart Angioplasty Research Team: Comparison Between P2Y12 Antagonist Monotherapy vs Dual Antiplatelet Therapy in Patients Undergoing Implantation of Coronary Drug-Eluting Stents; ST = stent thrombosis; STOPDAPT = Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent; TICO = Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus-eluting Stent for Acute Coronary Syndrome; TIMI = Thrombolysis In Myocardial Infarction; TVR = target vessel revascularization; TWILIGHT = Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention.

guidelines (62). Although data on de-escalation from potent $P2Y_{12}$ inhibitors to clopidogrel, with or without guidance using PFT and genetic testing, are less robust among elderly patients, this may also represent a treatment option (20). Differently, in elderly patients with HBR or with general frailty conditions, clopidogrel seems to be the most reasonable treatment option. Moreover, the strategy of shortening DAPT (i.e., $P2Y_{12}$ inhibitor discontinuation at 3 to 6 months in patients with ACS and 1 to 3 months in those with CCS), irrespective of choice of $P2Y_{12}$ inhibitor, now supported by a number of studies, can also be considered (9). Moreover, the shortest possible duration of antiplatelet treatment should be considered in the elderly, when used in combination with OACs (76). The adoption of new-generation drug-eluting stents would favor the use of short DAPT (1 to 6 months), as this strategy has been shown to be safe, including among patients ≥75 years of age (77). However, no dedicated randomized trials have compared a very short versus a longer DAPT regimen in patients with HBR. The MASTER DAPT (Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation With an Abbreviated Versus Standard DAPT Regimen) randomized trial (NCT03023020) will compare an abbreviated (1 month) versus a standard duration of antiplatelet therapy in patients with HBR, including elderly patients, and will provide important insights on the optimal duration of antiplatelet therapy after newer generation stent in this challenging population (78).

At 1 year after ACS and/or PCI or in patients with other CCS, several options for CAD prevention can be

CENTRAL ILLUSTRATION **Antithrombotic Strategies to Minimize the Risk for Bleeding in Elderly Patients With Acute Coronary Syndromes**



Capranzano, P. et al. J Am Coll Cardiol Intv. 2021;14(7):723–38.

adopted. However, currently aspirin represents the cornerstone of therapy in patients with stable CAD, especially among elderly patients (i.e., ≥75 years). Despite the ischemic benefit of extended DAPT or rivaroxaban 2.5 mg-based dual-pathway inhibition, this is counterbalanced by increased bleeding risk. These 2 strategies are endorsed by European guidelines in patients at moderate to high ischemic risk if HBR status is ruled out (62). However, their use in the elderly should be considered only after careful assessment in light of their high bleeding potential. In particular, the benefit of these more intensive long-term secondary prevention strategies may be questionable among the frailest and oldest subpopulation, such as those residing in nursing homes. Indeed, despite in these latter subgroups the available evidence would suggest a potential clinical benefit associated with enhanced secondary cardiovascular prevention regimens after myocardial infarction, the overall harm of more aggressive antithrombotic treatment is likely to overcome the expected benefit in frailer elderly patients, regardless of specific risk scores (79). Finally, $P2Y_{12}$ monotherapy beyond 1 year post-ACS may represent an attractive alternative option to conventional treatment with aspirin to further reduce ischemic events (69). Moreover, $P2Y_{12}$ monotherapy will be compared with standard long-term DAPT 1 year after ACS in patients at high ischemic and high bleeding risk, who may include elderly patients (80). Therefore, although the best evidence-based clinical judgment should currently guide decision making in elderly patients, further studies are warranted to specifically assess the impact of emerging antithrombotic strategies in elderly patients with CAD.

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REFERENCES

1. Benjamin EJ, Muntner P, Alonso A, et al. Heart disease and stroke statistics-2019 update: a report from the american heart association. Circulation 2019;139:e56–528.

2. Capodanno D, Angiolillo DJ. Antithrombotic therapy in the elderly. J Am Coll Cardiol 2010;56:1683–92.

3. Andreotti F, Rocca B, Husted S, et al. Antithrombotic therapy in the elderly: expert position paper of the European Society of Cardiology Working Group on Thrombosis. Eur Heart J 2015;36:3238–49.

4. Capodanno D, Huber K, Mehran R, et al. Management of antithrombotic therapy in atrial fibrillation patients undergoing PCI: *JACC* state-of-the-art review. J Am Coll Cardiol 2019;74:83–99.

5. Mari D, Ogliari G, Castaldi D, Vitale G, Bollini EM, Lio D. Hemostasis and ageing. Immun Ageing 2008;5:12.

6. Brandes RP, Fleming I, Busse R. Endothelial aging. Cardiovasc Res 2005;66:286–94.

7. Iyer KS, Dayal S. Modulators of platelet function in aging. Platelets 2020;31:474–82.

8. Veltkamp R, Rizos T, Horstmann S. Intracerebral bleeding in patients on antithrombotic agents. Semin Thromb Hemost 2013;39:963–71.

9. Capodanno D, Alfonso F, Levine GN, Valgimigli M, Angiolillo DJ. ACC/AHA versus ESC guidelines on dual antiplatelet therapy: *JACC* guideline comparison. J Am Coll Cardiol 2018;72:2915–31.

10. Ikeda Y, Shimada K, Teramoto T, et al. Low-dose aspirin for primary prevention of cardiovascular events in Japanese patients 60 years or older with atherosclerotic risk factors: a randomized clinical trial. JAMA 2014;312:2510–20.

11. McNeil JJ, Wolfe R, Woods RL, et al. Effect of aspirin on cardiovascular events and bleeding in the healthy elderly. N Engl J Med 2018;379:1509–18.

12. McNeil JJ, Nelson MR, Woods RL, et al. Effect of aspirin on all-cause mortality in the healthy elderly. N Engl J Med 2018;379:1519–28.

13. McNeil JJ, Woods RL, Nelson MR, et al. Effect of aspirin on disability-free survival in the healthy elderly. N Engl J Med 2018;379:1499–508.

14. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019;74:e177–232.

15. Antithrombotic Trialists' (ATT) Collaboration, Baigent C, Blackwell L, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet 2009;373:1849–60.

16. García Rodríguez LA, Hernández-Díaz S, de Abajo FJ. Association between aspirin and upper gastrointestinal complications: systematic review of epidemiologic studies. Br J Clin Pharmacol 2001;52:563–71.

17. Angiolillo DJ, Bhatt DL, Lanza F, et al. Pharmacokinetic/pharmacodynamic assessment of a novel, pharmaceutical lipid-aspirin complex: results of a randomized, crossover, bioequivalence study. J Thromb Thrombolysis 2019;48:554–62.

18. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK, for the Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001;345:494–502.

19. Silvain J, Cayla G, Hulot JS, et al. High on-thienopyridine platelet reactivity in elderly coronary patients: the SENIOR-PLATELET study. Eur Heart J 2012;33:1241–9.

20. Sibbing D, Aradi D, Alexopoulos D, et al. Updated expert consensus statement on platelet function and genetic testing for guiding $P2Y_{12}$ receptor inhibitor treatment in percutaneous coronary intervention. J Am Coll Cardiol Intv 2019;12:1521–37.

21. Angiolillo DJ, Capodanno D, Danchin N, et al. Derivation, validation, and prognostic utility of a prediction rule for nonresponse to clopidogrel: the ABCD-GENE score. J Am Coll Cardiol Intv 2020;13:606–17.

22. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001–15.

23. Wrishko RE, Ernest CS II, Small DS, et al. Population pharmacokinetic analyses to evaluate the influence of intrinsic and extrinsic factors on exposure of prasugrel active metabolite in TRITON-TIMI 38. J Clin Pharmacol 2009;49:984–98.

24. Erlinge D, Gurbel PA, James S, et al. Prasugrel 5 mg in the very elderly attenuates platelet inhibition but maintains noninferiority to prasugrel 10 mg in nonelderly patients: the GENERATIONS trial, a pharmacodynamic and pharmacokinetic study in stable coronary artery disease patients. J Am Coll Cardiol 2013;62:577–83.

25. Roe MT, Goodman SG, Ohman EM, et al. Elderly patients with acute coronary syndromes managed without revascularization: insights into the safety of long-term dual antiplatelet therapy with reduced-dose prasugrel versus standard-dose clopidogrel. Circulation 2013;128:823–33.

26. Savonitto S, Ferri LA, Piatti L, et al. Comparison of reduced-dose prasugrel and standard-dose clopidogrel in elderly patients with acute coronary syndromes undergoing early percutaneous revascularization. Circulation 2018;137:2435–45.

27. Cayla G, Cuisset T, Silvain J, et al. Platelet function monitoring to adjust antiplatelet therapy in elderly patients stented for an acute coronary syndrome (ANTARCTIC): an open-label, blinded-endpoint, randomised controlled superiority trial. Lancet 2016;388:2015–22.

28. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361:1–13.

29. Husted S, James S, Becker RC, et al. Ticagrelor versus clopidogrel in elderly patients with acute coronary syndromes: a substudy from the prospective randomized Platelet Inhibition and Patient Outcomes (PLATO) trial. Circ Cardiovasc Qual Outcomes 2012;5:680–8.

30. Gimbel M, Qaderdan K, Willemsen L, et al. Clopidogrel versus ticagrelor or prasugrel in patients aged 70 years or older with non-ST-elevation acute coronary syndrome (POPular AGE): the randomised, open-label, non-inferiority trial. Lancet 2020;395:1374–81.

31. Schmucker J, Fach A, Mata Marin LA, et al. Efficacy and safety of ticagrelor in comparison to clopidogrel in elderly patients with ST-segment-elevation myocardial infarctions. J Am Heart Assoc 2019;8:e012530.

32. Szummer K, Montez-Rath ME, Alfredsson J, et al. Comparison between ticagrelor and clopidogrel in elderly patients with an acute coronary syndrome—insights from the SWEDEHEART registry. Circulation 2020;42:1700–8.

33. Capranzano P, Angiolillo DJ. Tailoring $P2Y_{12}$ inhibiting therapy in elderly patients with myocardial infarction undergoing primary percutaneous coronary intervention. J Am Heart Assoc 2019;8:e014000.

34. Capranzano P, Angiolillo DJ. Ticagrelor or clopidogrel in elderly patients with myocardial infarction: when the choice makes the difference. Circulation 2020;142:1709–12.

35. Menichelli M, Neumann FJ, Ndrepepa G, et al. Age- and weight-adapted dose of prasugrel versus standard dose of ticagrelor in patients with acute

coronary syndromes: results from a randomized trial. Ann Intern Med 2020;173:436–44.

36. Mauri L, Kereiakes DJ, Yeh RW, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. N Engl J Med 2014;371:2155–66.

37. Bonaca MP, Bhatt DL, Cohen M, et al. Long-term use of ticagrelor in patients with prior myocardial infarction. N Engl J Med 2015;372:1791–800.

38. Steg PG, Bhatt DL, Simon T, et al. Ticagrelor in patients with stable coronary disease and diabetes. N Engl J Med 2019;381:1309–20.

39. Yeh RW, Secemsky EA, Kereiakes DJ, et al. Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention. JAMA 2016;315:1735–49.

40. Capodanno D, Bhatt DL, Eikelboom JW, et al. Dual-pathway inhibition for secondary and tertiary antithrombotic prevention in cardiovascular disease. Nat Rev Cardiol 2020;17:242–57.

41. Andreotti F, Testa L, Biondi-Zoccai GG, Crea F. Aspirin plus warfarin compared to aspirin alone after acute coronary syndromes: an updated and comprehensive meta-analysis of 25,307 patients. Eur Heart J 2006;27:519–26.

42. Mega JL, Braunwald E, Wiviott SD, et al. Rivaroxaban in patients with a recent acute coronary syndrome. N Engl J Med 2012;366:9–19.

43. Eikelboom JW, Connolly SJ, Bosch J, et al. Rivaroxaban with or without aspirin in stable cardiovascular disease. N Engl J Med 2017;377:1319–30.

44. Capodanno D, Morice MC, Angiolillo DJ, et al. Trial design principles for patients at high bleeding risk undergoing PCI: *JACC* scientific expert panel. J Am Coll Cardiol 2020;76:1468–83.

45. Khan SU, Singh M, Valavoor S, et al. Dual Antiplatelet therapy after percutaneous coronary intervention and drug-eluting stents: a systematic review and network meta-analysis. Circulation 2020;142:1425–36.

46. Gargiulo G. To encourage individualized dual antiplatelet therapy duration after drug-eluting stent implantation: a new page of an intriguing book. J Am Coll Cardiol Intv 2018;11:444–7.

47. Lee SY, Hong MK, Palmerini T, et al. Short-term versus long-term dual antiplatelet therapy after drug-eluting stent implantation in elderly patients: a meta-analysis of individual participant data from 6 randomized trials. J Am Coll Cardiol Intv 2018;11:435–43.

48. Piccolo R, Magnani G, Ariotti S, et al. Ischaemic and bleeding outcomes in elderly patients undergoing a prolonged versus shortened duration of dual antiplatelet therapy after percutaneous coronary intervention: insights from the PRODIGY randomised trial. EuroIntervention 2017;13:78–86.

49. Angiolillo DJ, Rollini F, Storey RF, et al. International expert consensus on switching platelet $P2Y_{12}$ receptor-inhibiting therapies. Circulation 2017;136:1955–75.

50. Kim HS, Kang J, Hwang D, et al. Prasugrel-based de-escalation of dual antiplatelet therapy after percutaneous coronary intervention in patients with acute coronary syndrome (HOST-REDUCE-POLYTECH-ACS): an open-label, multicentre, non-inferiority randomised trial. Lancet 2020;396:1079–89.

51. Sibbing D, Aradi D, Jacobshagen C, et al. Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS): a randomized, open-label, multicenter trial. Lancet 2017;390:1747–57.

52. Sibbing D, Gross L, Trenk D, et al. Age and outcomes following guided de-escalation of antiplatelet treatment in acute coronary syndrome patients undergoing percutaneous coronary intervention: results from the randomized TROPICAL-ACS trial. Eur Heart J 2018;39:2749–58.

53. Claassens DMF, Vos GJA, Bergmeijer TO, et al. A genotype-guided strategy for oral $P2Y_{12}$ inhibitors in primary PCI. N Engl J Med 2019;381:1621–31.

54. Capodanno D, Mehran R, Valgimigli M, et al. Aspirin-free strategies in cardiovascular disease and cardioembolic stroke prevention. Nat Rev Cardiol 2018;15:480–96.

55. Capodanno D, Di Maio M, Greco A, et al. Safety and efficacy of double antithrombotic therapy with non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation undergoing percutaneous coronary intervention: a systematic review and meta-analysis. J Am Heart Assoc 2020;9:e017212.

56. Gibson CM, Mehran R, Bode C, et al. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. N Engl J Med 2016;375:2423–34.

57. Cannon CP, Bhatt DL, Oldgren J, et al. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. N Engl J Med 2017;377:1513–24.

58. Lopes RD, Heizer G, Aronson R, et al. Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation. N Engl J Med 2019;380:1509–24.

59. Vranckx P, Valgimigli M, Eckardt L, et al. Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen after successful coronary stenting in patients with atrial fibrillation (ENTRUST-AF PCI): a randomised, open-label, phase 3b trial. Lancet 2019;394:1335–43.

60. ten Berg JM, Steg PG, Bhatt DL, et al. Comparison of the effect of age ($<$ 75 versus $\geq$ 75) on the efficacy and safety of dual therapy (dabigatran + clopidogrel or ticagrelor) versus triple therapy (warfarin + aspirin + clopidogrel or ticagrelor) in patients with atrial fibrillation after percutaneous coronary intervention (from the RE-DUAL PCI trial). Am J Cardiol 2020;125:735–43.

61. Angiolillo DJ, Bhatt DL, Cannon CP, et al. Antithrombotic therapy in patients with atrial fibrillation treated with oral anticoagulation undergoing percutaneous coronary intervention: a North American perspective: 2021 update. Circulation 2021;143:583–96.

62. Collet JP, Thiele H, Barbato E, et al. 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J 2020;32:2999–3054.

63. Vranckx P, Valgimigli M, Jüni P, et al. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. Lancet 2018;392:940–9.

64. Tomaniak M, Chichareon P, Modolo R, et al. Ticagrelor monotherapy beyond one month after PCI in ACS or stable CAD in elderly patients: a prespecified analysis of the GLOBAL LEADERS trial. EuroIntervention 2020;15:e1605–14.

65. Hahn JY, Song YB, Oh JH, et al. Effect of $P2Y_{12}$ inhibitor monotherapy vs dual antiplatelet therapy on cardiovascular events in patients undergoing percutaneous coronary intervention: the SMART-CHOICE randomized clinical trial. JAMA 2019;321:2428–37.

66. Watanabe H, Domei T, Morimoto T, et al. Effect of 1-month dual antiplatelet therapy followed by clopidogrel vs 12-month dual antiplatelet therapy on cardiovascular and bleeding events in patients receiving PCI: the STOPDAPT-2 randomized clinical trial. JAMA 2019;321:2414–27.

67. Mehran R, Baber U, Sharma SK, et al. Ticagrelor with or without aspirin in high-risk patients after PCI. N Engl J Med 2019;381:2032–42.

68. Kim BK, Hong SJ, Cho YH, et al. Effect of ticagrelor monotherapy vs ticagrelor with aspirin on major bleeding and cardiovascular events in patients with acute coronary syndrome: the TICO randomized clinical trial. JAMA 2020;323:2407–16.

69. Franzone A, McFadden E, Leonardi S, et al. Ticagrelor alone versus dual antiplatelet therapy from 1 month after drug-eluting coronary stenting. J Am Coll Cardiol 2019;74:2223–34.

70. Franzone A, McFadden EP, Leonardi S, et al. Ticagrelor alone or conventional dual antiplatelet therapy in patients with stable or acute coronary syndromes. EuroIntervention 2020;16:627–33.

71. Moayyedi P, Eikelboom JW, Bosch J, et al. Pantoprazole to prevent gastroduodenal events in patients receiving rivaroxaban and/or aspirin in a randomized, double-blind, placebo-controlled trial. Gastroenterology 2019;157:403–12.e5.

72. Montalto C, Crimi G, Morici N, et al. Bleeding risk prediction in elderly patients managed invasively for acute coronary syndromes: external validation of the PRECISE-DAPT and PARIS scores. Int J Cardiol 2021;328:22–8.

73. Urban P, Mehran R, Colleran R, et al. Defining high bleeding risk in patients undergoing percutaneous coronary intervention. Circulation 2019;140:240–61.

74. Corpataux N, Spirito A, Gragnano F, et al. Validation of high bleeding risk criteria and definition as proposed by the academic research consortium for high bleeding risk. Eur Heart J 2020;41:3743–9.

75. Costa F, van Klaveren D, James S, et al. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. Lancet 2017;389:1025–34.

76. Fox KAA, Velentgas P, Camm AJ, et al. Outcomes Associated with oral anticoagulants plus antiplatelets in patients with newly diagnosed atrial fibrillation. JAMA Netw Open 2020;3:e200107.

77. Varenne O, Cook S, Sideris G, et al. Drug-eluting stents in elderly patients with coronary artery disease (SENIOR): a randomised single-blind trial. Lancet 2018;391:41–50.

78. Frigoli E, Smits P, Vranckx P, et al. Design and rationale of the management of high bleeding risk patients post bioresorbable polymer coated stent implantation with an abbreviated versus standard DAPT regimen (MASTER DAPT) study. Am Heart J 2019;209:97–105.

79. Zullo AR, Mogul A, Corsi K, et al. Association between secondary prevention medication use and outcomes in frail older adults after acute myocardial infarction. Circ Cardiovasc Qual Outcomes 2019;12:e004942.

80. Li Y, Jing Q, Wang B, et al. Extended antiplatelet therapy with clopidogrel alone versus clopidogrel plus aspirin after completion of 9- to 12-month dual antiplatelet therapy for acute coronary syndrome patients with both high bleeding and ischemic risk. Rationale and design of the OPT-BIRISK double-blinded, placebo-controlled randomized trial. Am Heart J 2020;228:1–7.

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